PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Community-based HPV self-collection vs. visual inspection with acetic acid in Uganda: a cost-effectiveness analysis of the ASPIRE trial
AUTHORS	Mezei, Alex; Pedersen, Heather; Sy, Stephen; Regan, Catherine; Mitchell-Foster, Sheona; Byamugisha, Josaphat; Sekikubo, Musa; Armstrong, Heather; Rawat, Angeli; Singer, Joel; Ogilvie, Gina; Kim, Jane; Campos, Nicole

VERSION 1 – REVIEW

REVIEWER	Adolf Kofi Awua Cellular and Clinical Research Centre, Radiological and Medical Sciences Research Institute Ghana
REVIEW RETURNED	21-Nov-2017

GENERAL COMMENTS	Reviewer's Comment Manuscript ID: bmjopen-2017-020484 Title: Community-based HPV self-collection vs. visual inspection with acetic acid in Uganda: a cost-effectiveness analysis of the ASPIRE trial. Article Type: Research I commend Mezei et al., for undertaken this research work, to provide additional information in respect of the ASPIRE TRIAL, specifically proving information on the cost-effectiveness of the screening strategies studied therein. The authors considered the two screening strategies for cervical cancer in the ASPIRE trial as well as a strategy they innovated, which was an HPV screen-and-treat strategy ("HPV-ST") involving community-based self-collected HPV testing followed by treatment for all HPV-positive women at the clinic, in a Monte Carlo simulation model of HPV infection and cervical cancer. The implication of findings which indicated that HPV-ST was more cost-effective compared to the strategies, community-based self-collected HPV with VIA triage (HPV-VIA) and VIA screening, in that order, are significant for planning cervical cancer prevention screening programmes in low-middle income countries. However, I suggest that the authors carefully consider the following comments in revising their manuscript. General comments

	1. The technical appendix was detailed enough to inform a reader, of this manuscript, of what the context and limitation of the study were. 2. CHEERS checklist item "Choice of model (15) – Describe and give reasons for the specific type of decision-analytical model used". Providing a figure to show model structure is strongly recommended, is outstanding. 3. CHEERS checklist item "20b Model-based economic evaluation: Describe the effects on the results of uncertainty for all input parameters, and uncertainty related to the structure of the model and assumptions" has a reference page which is not under the results section (page 6-line 25-38; and page 7-line 1-3 Specific comments Page 4, Lines 22-24: I suggest to delete "Despite the success of cytology-based screening in HICs," and move "there are significant barriers to access, implementation and quality assurance in LMICs." To line 13 on the same page, where issues on LMIC was indicated. The objective of the study was clearly stated in the abstract (which is, ".....to evaluate the cost-effectiveness of the ASPIRE trial, conducted in Kisenyi, Uganda in April 2014 (n=500)."), however, it was not clearly so in the introduction, (which is, "To inform policy, we conducted a cost-effectiveness analysis of a randomized trial run …."); therefore a suggest a modification of the latter to reflect that in the abstract. Page 5, line 34-35: Replace "….. places of work that were between the ages of 30 and 65, lived….." with "….. places of work who were between the ages of 30 and 65 years, lived….." Page 5: Section on The ASPIRE Trial: it will be good to indicate that at the time of enrolment, consenting women were randomized into the different arms of the ASPIRE trial and that the trial received ethical clearance. Page 6, line 35-36: If possible provide more information or make reference to where this information, in respect of "We set a range of plausible bounds for these uncertain model parameters" may be found. Page 8, line 50: It will be good to indicate the reasons/bases of the assumption made for screening coverage in the base case, as 70%." I did not find the bases in the technical appendix. Was it based on the ASPIRE trial's or another study or it is a desirable/accepted minimum coverage of a successful screening programme? Please note that in our nonrandomized study, but which was similar in respect of strategy, home-based self-specimen collection for HPV testing versus a hospital based Pap smear testing in a LMIC, the overall screening coverage was 60.4%; BMC Public Health (2017) 17:736 DOI 10.1186/s12889-017-4631-y. Page 9, lines 15-16: in respect of costs elements, indicating that detail are available in technical appendix at an earlier part of the section will help the reader avoid wondering what the details or expecting to see them herein. a) I hope the equipment cost excludes additional equipment laboratory, if any, and also considered the importation, installation

	costs, and maintenance cost of the equipment? b) Was there a Cost for CHW reaching the women at home or was it included in the community mobilisation cost or the cost associated with CHW? A LMIC wanting to start from scratch, such a strategy in screen programme, will need to understand the detail of such cost to be certain of their decision. Table 2, Table 4: replace “Relative cancer reductiona” with “Relative cancer risk reductiona” Double presentation of the same data in a table and figure is not the best, I suggest to modify to avoid such. Example, delete the column “Discounted lifetime cost per woman” and “Discounted life expectancy” from the table 2 and present as supplementary table. Then present the range in brackets instead of the ICER on the figure 2.

REVIEWER	Joel Fokom Domgue Department of Obstetrics and Gynecology, University Hospital Center, Yaounde, Cameroon.
REVIEW RETURNED	08-Dec-2017

GENERAL COMMENTS	Thank you to the authors for opportunity to review their manuscript entitled “Community-based HPV self-collection vs. visual inspection with acetic acid in Uganda: a cost-effectiveness analysis of the ASPIRE trial”. Economic evaluations of health interventions are critical to help decision makers in the choice of the intervention (a screening strategy in this case) they want to implement in a given setting based on resource available, especially in limited resource settings. The research question is relevant and the manuscript is well written. However, I have some major concerns I would like the authors to address. I think that a major limitation is the inability of the study to assess the impact of the interventions on the ultimate health outcomes of cervical cancer incidence and mortality. The “surrogate” outcome used by authors is reduction in cervical cancer risk, and thus incremental cost-effectiveness ratios (ICERs) calculated here may not be as accurate as expected. On the other hand, it is not clear to me if in their economic analysis, authors accounted for the limited workforce in the local health units, especially with regard to treatment with cryotherapy when assessing the HPV-ST strategy, as well as the VIA strategy. Indeed, in the scenario where all HPV positive (or VIA positive) women have to be treated in real-world conditions (as opposed to conditions of a clinical trial), it is unlikely that providers in local health units will be sufficient in quantity and in quality to offer treatment in a timely manner to all eligible women, while performing their daily activities. This important factor from my point of view, may have an impact on the wait time for women attending the health facility for treatment (cryotherapy), the number of treatment machine available at the health facility (in the case there are many providers trained), the availability of additional rooms in the health facility to allow providers to offer treatment to women (in the case there are many providers trained and available to treat eligible women separately but at the same time), the continuous provision of services offered to patients coming to the health facility for other health issues, etc… From that perspective, the use of data from a clinical trial to assess cost-effectiveness of health interventions may raise concerns about the

	realistic assessment and accuracy of this economic analysis. In the “strengths and limitations of the study” heading, it writes: “The model used in this study was unable to capture the health and economic benefits of screening for N. gonorrhoeae and C. trachomatis, which occurred along with cervical cancer screening in the ASPIRE trial”. This is not appropriate here as the main objective of this study was not to assess the benefits of NG or CT, nor to evaluate how cost-effective the integration of these intervention might be. However, it might be challenging to separate the expenses (including time for sample collection, etc…) related to NGCT screening from those related exclusively to CC screening in this trial (which adds complexity to the economic analysis of these data), and I would suggest that authors describe in more details in the relevant sections of the manuscript, how they did separate expenses related to these screening (NGCT vs CC), and how they did account for this “possible confusion” in their analyzes. Another limitation of using data from a randomized trial is that women included in the trial were those who had access to a cell phone, which might hardly be the case in remote and rural areas, where most women in need of screening might live. How did the authors account for this in the analyzes? I strongly suggest to authors that some analyses should be rerun, results redrawn and the discussion adjusted in the light of these comments. There are many other minor comments, some of which include the following. In the abstract, I would suggest to the authors to separate the “background” from the “study objectives”. Page 8 line 40, it writes: “For the base case analysis, we assumed screening coverage of 70%. What is the rationale for this assumption? Page 9, line 20 to 21: it writes “in several cases, cost data were not available”. Could you give in more detail the situations where cost data were not available from the ASPIRE study, and which studies you used to estimate the cost in these situations? Page 9, line 32: you are assuming a 3% interest rate. On what basis are you making this assumption?

VERSION 1 – AUTHOR RESPONSE

Reviewer 1 (Adolf Kofi Awua):

1. The technical appendix was detailed enough to inform a reader, of this manuscript, of what the context and limitation of the study were.

We thank the reviewer for the positive feedback.

2. CHEERS checklist item “Choice of model (15) – Describe and give reasons for the specific type of decision-analytical model used”. Providing a figure to show model structure is strongly recommended, is outstanding.

We have inserted the model schematic into the manuscript as Figure 1. As mentioned in the “CHEERS checklist”, we will request permission to reproduce this figure if the manuscript is accepted because a similar figure has been published previously in the American Journal of Epidemiology (AJE) by authors on this manuscript. The AJE’s policy is that requests to reproduce figures can only be made once a manuscript has been accepted for publication.

p. 6

Figure 1. Model schematic

3. CHEERS checklist item “20b Model-based economic evaluation: Describe the effects on the

results of uncertainty for all input parameters, and uncertainty related to the structure of the model and assumptions" has a reference page which is not under the results section (page 6-line 25-38; and page 7-line 1-3
Thank you for bringing our attention to this error. This has been amended.
4. Page 4, Lines 22-24: I suggest to delete "Despite the success of cytology-based screening in HICs," and move "there are significant barriers to access, implementation and quality assurance in LMICs." To line 13 on the same page, where issues on LMIC was indicated.
The suggested changes have been made.
p.4 "Despite the success of cytology-based screening in HICs, T There are significant barriers to access, implementation and quality assurance for cytology-based screening in LMICs."
5. The objective of the study was clearly stated in the abstract (which is, ".....to evaluate the cost-effectiveness of the ASPIRE trial, conducted in Kisenyi, Uganda in April 2014 (n=500)."), however, it was not clearly so in the introduction, (which is, "To inform policy, we conducted a cost-effectiveness analysis of a randomized trial run …."); therefore a suggest a modification of the latter to reflect that in the abstract.
The wording of the introduction has been amended to enhance clarity.

p.4 "To inform future policy, Therefore, our objective was to evaluate the cost-effectiveness of we conducted a cost-effectiveness analysis of a randomized trial run by the Advances in Screening and Prevention of Reproductive Cancers (ASPIRE) Project, which compared community-based self-collected HPV testing to clinic-based VIA in Uganda.11
"
6. Page 5, line 34-35: Replace "….. places of work that were between the ages of 30 and 65, lived….." with "….. places of work who were between the ages of 30 and 65 years, lived….."
This grammatical error has been amended.
p.5 "For the trial, community health workers (CHWs) recruited 500 women at their homes or places of work that who were between the ages of 30 and 65…"
7. Page 5: Section on The ASPIRE Trial: it will be good to indicate that at the time of enrolment, consenting women were randomized into the different arms of the ASPIRE trial and that the trial received ethical clearance.
These suggested amendments were made.
p.5 "Ethics were approved by the University of British Columbia and Makerere University."
p.5 "At the time of enrolment, consenting women were randomized into either HPV selfcollection with VIA triage for HPV-positive women ("HPV-VIA") or VIA screen and treat ("VIA")."
8. Page 6, line 35-36: If possible provide more information or make reference to where this information, in respect of "We set a range of plausible bounds for these uncertain model parameters" may be found.

We have added nine new tables to the technical appendix that show the range of plausible bounds that were sampled from (technical appendix, pages 10-26). In addition, two citations have been added so that the reader knows what paper to reference if they wish to see a more detailed description of the calibration process.
p.7 "We set a range of plausible bounds for these uncertain model parameters and then randomly sampled from a uniform distribution across this range of values.10, 12 The range of plausible bounds that was sampled from for each variable is shown in the technical appendix."
9. Page 8, line 50: It will be good to indicate the reasons/bases of the assumption made for screening coverage in the base case, as 70%." I did not find the bases in the technical appendix. Was it based on the ASPIRE trial's or another study or it is a desirable/accepted minimum coverage of a successful screening programme? Please note that in our nonrandomized study, but which was similar in respect of strategy, home-based self-specimen collection for HPV testing versus a hospital based Pap smear testing in a LMIC, the overall screening coverage was 60.4%; BMC Public Health (2017) 17:736 DOI 10.1186/s12889-017-4631-y.

This assumption was made to maintaining consistency with previous modelling-based studies.
10,27 70% has been used because it is felt to be a marker of an organized screening program with reasonably desirable coverage levels (i.e. at least 70% screened). Please note that screening coverage was varied in sensitivity analysis to levels of 40%, 55%, 85% and 100% without any change to the rank ordering of strategies or ICERs.
10. Page 9, lines 15-16: in respect of costs elements, indicating that detail are available in technical appendix at an earlier part of the section will help the reader avoid wondering what the details or expecting to see them herein.
The manuscript states in the first sentence of the section "cost data" within the methods that "Cost data and time estimates are described extensively in the Technical Appendix and presented in Table 1."
11. a) I hope the equipment cost excludes additional equipment laboratory, if any, and also considered the importation, installation costs, and maintenance cost of the equipment?
As outlined in the technical appendix laboratory costs for HPV testing were derived from START-UP costs, whereas biopsy costs were derived from ASPIRE data. In both cases, laboratory costs include lab staff, lab supply and lab equipment costs that were specific to the indicated test. The footnote on Table 4 in the technical appendix has been amended to clarify this.
We have elaborated on importation, installation and maintenance costs in the technical appendix.

Technical appendix, p.5 (footnote "e"): "Laboratory costs include supplies, equipment and staffing costs specific to the indicated test."
Technical appendix, p.4: "The total cost, amortized cost, estimated lifespan and cost per procedure for each item is listed in Table 5. There were no importation costs as all equipment was purchased in Uganda. ASPIRE was never billed for installation, so it was assumed that this was included with in the amount paid for equipment. There were no costs for maintenance of equipment in the 3 months of the APSIRE trial."
12. b) Was there a Cost for CHW reaching the women at home or was it included in the community mobilisation cost or the cost associated with CHW? A LMIC wanting to start from scratch, such a strategy in screen programme, will need to understand the detail of such cost to be certain of their decision.
The cost for CHWs reaching women at home is included in the CHW time cost. The paragraph on CHW time costs in the technical appendix has been amended to state this more explicitly.
Techincal appendix p.3 "Table 4 states the CHW time cost for each woman enrolled in the trial. In the ASPIRE trial, CHW time costs included the following:s were responsible for visiting women at their homes or places of work to enroll them in the trial, conducting a demographic survey, instructing women on self-collection, transporting HPV samples, and calling women to deliver results and remind women to attend VIA."
13. Table 2, Table 4: replace "Relative cancer reduction" with "Relative cancer risk reduction"
The suggested change has been made.
14. Double presentation of the same data in a table and figure is not the best, I suggest to modify to avoid such. Example, delete the column "Discounted lifetime cost per woman" and "Discounted life expectancy" from the table 2 and present as supplementary table. Then present the range in brackets instead of the ICER on the figure 2.
The columns "discounted lifetime cost per woman" and "discounted life expectancy" have been deleted from Table 2. A new table including this information has been added as Table 6 to the technical appendix. We have opted to leave the ICER in brackets in figure 2. The range for the dominated strategies is now in Table 6 of the technical appendix and we feel that keeping the ICERs of the dominant strategies in brackets in figure 2 provides a nice visual representation of the results for the reader.

Reviewer 2 (Joel Fokom Domgue)

1. Thank you to the authors for opportunity to review their manuscript entitled “Communitybased HPV self-collection vs. visual inspection with acetic acid in Uganda: a cost-effectiveness analysis of the ASPIRE trial”. Economic evaluations of health interventions are critical to help decision makers in the choice of the intervention (a screening strategy in this case) they want to implement in a given setting based on resource available, especially in limited resource settings. The research question is relevant and the manuscript is well written.

We thank the reviewer for this positive feedback.

2. However, I have some major concerns I would like the authors to address. I think that a major limitation is the inability of the study to assess the impact of the interventions on the ultimate health outcomes of cervical cancer incidence and mortality. The “surrogate” outcome used by authors is reduction in cervical cancer risk, and thus incremental cost-effectiveness ratios (ICERs) calculated here may not be as accurate as expected.

ICERS are not derived from the “surrogate” outcome reduction in cervical cancer risk. Rather, ICERs are derived by dividing the marginal cost (i.e. discounted per women cost) by the marginal benefit (discounted life expectancy) of a screening strategy compared to the next most costly strategy, after eliminating strategies that are dominated (defined as either more costly and less effective or having a higher ICER than more effective strategies). This yields an ICER in the units of dollars per year of life saved. Please note that life expectancy incorporates both cervical cancer incidence and mortality, and that our model has been calibrated to agespecific cervical cancer incidence in Uganda (as specified in the methods, sub-heading “mathematical simulation model”). We have amended the paragraph in the methods that defines ICERs to enhance clarity.

Additionally, “llifetime risk” is the cumulative lifetime incidence of cervical cancer. We have amended the paragraph in the methods that states lifetime risk as a primary outcome to specify this.

p.5 “The primary outcomes were the incremental cost-effectiveness ratio (ICER) and percent reduction in lifetime cervical cancer risk (i.e. cumulative lifetime cervical cancer incidence). ICERs are defined as the marginal cost (discounted per women cost) divided by the marginal benefit (discounted life expectancy) of a screening strategy compared to the next most costly strategy, after eliminating strategies that are dominated (defined as either more costly and less effective or having a higher ICER than more effective strategies).”

3. On the other hand, it is not clear to me if in their economic analysis, authors accounted for the limited workforce in the local health units, especially with regard to treatment with cryotherapy when assessing the HPV-ST strategy, as well as the VIA strategy. Indeed, in the scenario where all HPV positive (or VIA positive) women have to be treated in real-world conditions (as opposed to conditions of a clinical trial), it is unlikely that providers in local health units will be sufficient in quantity and in quality to offer treatment in a timely manner to all eligible women, while performing their daily activities. This important factor from my point of view, may have an impact on the wait time for women attending the health facility for treatment (cryotherapy), the number of treatment machine available at the health facility (in the case there are many providers trained), the availability of additional rooms in the health facility to allow providers to offer treatment to women (in the case there are many providers trained and available to treat eligible women separately but at the same time), the continuous provision of services offered to patients coming to the health facility for other health issues, etc… From that perspective, the use of data from a clinical trial to assess cost-effectiveness of health interventions may raise concerns about the realistic assessment and accuracy of this economic analysis.

We agree with the reviewer that there would be an opportunity cost associated with increased utilization of midwives that is not captured due to the nature of randomized trials. However, there is also a potential benefit of using such a strategy, in that effectively triaging women at home with a self-collected HPV test delivered by a CHW might free up midwife resources for

other health care activities that are more taxed in the VIA strategy. We agree that we should be more explicit about the limited scope of this study, given that it is a cost-effectiveness analysis of a clinical trial, so we have amended the discussion to reflect this.
p.18 “In addition to limitations surrounding costing data, the trial setting limited the scope of this cost-effectiveness analysis. It is unclear how real-world human resource constraints might affect the cost-effectiveness of the different screening strategies through impact on women’s waiting time in typical primary care settings. Furthermore, decision makers will need to assess where limited health care provider time is best spent. It is of note that all the women in this study had access to a mobile phone. This may not be the case in rural and remote areas of Uganda, so novel screening approaches may need to be developed that would be more suitable for these locations.”
4. In the “strengths and limitations of the study” heading, it writes: “The model used in this study was unable to capture the health and economic benefits of screening for N. gonorrhoeae and C. trachomatis, which occurred along with cervical cancer screening in the ASPIRE trial”. This is not appropriate here as the main objective of this study was not to assess the benefits of NG or CT, nor to evaluate how cost-effective the integration of these intervention might be.
We have amended the wording to reflect that this was not a specific objective of the study.
p.18 “While it was not a stated objective of this study to evaluate the cost-effectiveness of N. gonorrhoeae and C. trachomatis screening, this was an integral part of the ASPIRE trial due to the hypothesis that efficiency gains could be achieved by bundling health interventions with overlapping infrastructure needs. Moving forward, developing models that can evaluate the integrated delivery of primary care services will be critical to assess the wider impacts of new health care delivery methods in low resource settings, as well as to capture potential synergies associated with packaging interventions.”
5. However, it might be challenging to separate the expenses (including time for sample collection, etc…) related to NGCT screening from those related exclusively to CC screening in this trial (which adds complexity to the economic analysis of these data), and I would suggest that authors describe in more details in the relevant sections of the manuscript, how they did separate expenses related to these screening (NGCT vs CC), and how they did account for this “possible confusion” in their analyzes.
We have clarified how the costs were excluded in the technical appendix. We performed explicit calculations to exclude NGCT costs from women’s time, supply and sample transport costs. For midwife, CHW, phone and programmatic costs, we assumed NGCT costs to be negligible. Given how robust the results were to extensive sensitivity analyses (including sensitivity analyses that varied direct medical costs), we do not feel it would be of added value to make minor cost adjustments to the cost variables that were not adjusted for NGCT screening.
Technical appendix p.2 Women’s time estimates “We excluded time estimates for NGCT screening and follow up for positive NGCT results.”
Technical appendix p.3 Midwife costs “We assumed midwives spent no extra time on NGCT screening. Midwives performed a total of 111 NGCT swabs, all of which occurred at the same time as the VIA. The extra time for the swab was estimated to be 2 minutes, compared to 20 minutes for a VIA and 30 minutes for cryotherapy. In ASPIRE, a total of 154 VIAs and 11 cryotherapies were performed, for a total of 3410 midwife minutes. Adding the extra time for an NGCT swab (222 minutes) to the total time spent by midwives on VIA and cryotherapy (3410 minutes), and then dividing by 222, yields a total proportion of midwife time spent on NGCT of 6.5%. This difference was felt to be negligible and falls within the range of sensitivity analyses on direct medical costs that had no effect on the rank ordering of strategies and only minimally affected ICERs.”
Technical appendix p.3 CHW costs “We assumed that no extra time was spent by the CHWs on NGCT screening. Research assistants involved in the trial estimated that the self-collection of an HPV and NGCT sample took an average of 5 minutes total, or 2.5 minutes per sample. CHWs

would enrol an average of 5 women per day during an 8 hour work day, half of which were randomized to VIA. This means that CHWs spent an extra 6.25 minutes out of an 8 hour day waiting for NGCT samples, or 1.3% of their time. This time difference was felt to be negligible and falls within the range of sensitivity analyses on direct medical costs that had no effect on the rank ordering of strategies and only minimally affected ICERs.
Technical appendix p.3-4 Phone costs "As only 10/500 women needed to be called about NGCT results, many of whom were being contacted for HPV results anyway, the phone costs associated with NGCT screening were assumed to be negligible."
Technical appendix p.4 Supply costs "We excluded the costs of extra swabs for NGCT testing from supply cost calculations."
Technical appendix p.4 Laboratory transport costs "In the ASPIRE trial, HPV and N. gonorrhea/C. trachomatis samples were transported by car to MBN laboratories for testing. ASPIRE grant reconciliation sheets detailed the number of trips taken to transport samples and the cost per trip. We multiplied these figures to come up with total transport costs for the trial, and then divided by the number of HPV and NGCT samples to come up with a transport cost per sample, as shown in table 4.
Technical appendix p.4 Programmatic costs "We assumed there were no additional programmatic costs associated with NGCT screening."
Technical appendix p.4 Equipment costs "As this equipment would be required with or without NGCT screening, no adjustment to cost data was made."
6. Another limitation of using data from a randomized trial is that women included in the trial were those who had access to a cell phone, which might hardly be the case in remote and rural areas, where most women in need of screening might live. How did the authors account for this in the analyzes? I strongly suggest to authors that some analyses should be rerun, results redrawn and the discussion adjusted in the light of these comments.
We agree that this affects the generalizability of our study. We have inserted a line in the limitations section in recognition of this.
p.4 "It is of note that all the women in this study had access to a mobile phone. This may not be the case in rural and remote areas of Uganda, so novel screening approaches may need to be developed that would be more suitable for these locations."
7. There are many other minor comments, some of which include the following. In the abstract, I would suggest to the authors to separate the "background" from the "study objectives".
The abstract has been amended in response to this feedback.
8. Page 8 line 40, it writes: "For the base case analysis, we assumed screening coverage of 70%. What is the rationale for this assumption?
This assumption was made to maintaining consistency with previous modelling-based studies.10,27 70% has been used because it is felt to be a marker of an organized screening program with reasonably desirable coverage levels (i.e. at least 70% screened). Please note that screening coverage was varied in sensitivity analysis to levels of 40%, 55%, 85% and 100% without any change to the rank ordering of strategies or ICERs.

9. Page 9, line 20 to 21: it writes "in several cases, cost data were not available". Could you give in more detail the situations where cost data were not available from the ASPIRE study, and which studies you used to estimate the cost in these situations?
We feel that we have been as explicit as possible about the situations in which ASPIRE cost data were not available and which studies we used to estimate the cost in these situations:
p.9 "In several cases, ASPIRE cost data was not available and we instead used costs from other studies. HPV self-collection test cost, supplies, HPV laboratory costs and cryotherapy equipment costs were informed from the PATH START-UP demonstration project in Uganda that used careHPV testing.9 Cancer treatment costs were derived from Campos et al.27
"
10. Page 9, line 32: you are assuming a 3% interest rate. On what basis are you making this

assumption?
This is based off World Health Organization guidelines for cost-effectiveness analysis as stated. Moreover, the original manuscript includes sensitivity analyses with discount rates of 0% and 5% (Table 3).
p.16 “In keeping with guidelines on cost-effectiveness analysis, we discounted all costs and future life years at a rate of 3% per year and evaluated costs from a societal perspective, including costs irrespective of the payer.

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VERSION 2 – REVIEW

REVIEWER	Adolf Kofi Awua Radiological and Medical Science Research Institute; Ghana
REVIEW RETURNED	08-Feb-2018

GENERAL COMMENTS	Manuscript ID: bmjopen-2017-020484-R1 Title: Community-based HPV self-collection vs. visual inspection with acetic acid in Uganda: a cost-effectiveness analysis of the ASPIRE trial. Article Type: Research

	I commend the author for making the efforts to amend their manuscript according to the reviewers' comments and responding appropriately. However, the following few minor comments, in my view, should be addressed. General Comments: I suggest the authors make a recommendation for the conduct of implementation study that should be designed for a cost-effectiveness analysis and for which the identified limitations in the current study are controlled for and one that will reflect a real-world situation as much as possible. Comments Abstract: Page 2: Some, particularly, the major limitations of the study, as identified in the comments of the second reviewer, need to be stated in the abstract. Page 7: lines 50-51: Replace "ASPIRE cost data was not available" with "ASPIRE cost data were not available". Page 16: "These results should assist in program planning to implement approaches to reduce the burden of cervical cancer globally, and catalyze the development of new studies and programmes." Is respect of the statement above, I suggest the authors are more specific with their recommendations. For example, which type of study and of what focus does the result of this study engender; which of the strategies considered in this study require further study to understand it contribution to reducing the burden of cervical cancer globally. Figure 1: Do all the three cervical cancer prevention methods apply at all three points indicated by the broken arrows? I guess not, therefore, I suggest the authors present separate boxes for each of the methods of prevention; screening, diagnosis and treatment, showing where each applies in the scheme of the natural history for clarity.

REVIEWER	Joel Fokom Domgue University Hospital Center, Yaounde, Cameroon
REVIEW RETURNED	13-Feb-2018

GENERAL COMMENTS	in the revised version of the manuscript, the authors properly addressed the concerns raised by the reviewers.

VERSION 2 – AUTHOR RESPONSE

Reviewer 1 (Adolf Kofi Awua):

1. I suggest the authors make a recommendation for the conduct of implementation study that should be designed for a cost-effectiveness analysis and for which the identified limitations in the current study are controlled for and one that will reflect a real-world situation as much as possible.

We agree that making a more specific recommendation would strengthen the paper. We have modified the text below:

p.16 "In 2012, over 230,000 women in LMICs died from cervical cancer, approximately 2,200 of whom were from Uganda.2 This study demonstrates that there are very cost-effective options that could significantly reduce morbidity and mortality attributable to cervical cancer.

Implementation studies on a larger scale— that would assess the effectiveness and costeffectiveness of community-based screening in the context of the Ugandan health system— are

warranted. Such studies will provide lessons for nascent screening programmes in low-resource settings with a high burden of cervical cancer. These results should assist in program planning to implement approaches to reduce the burden of cervical cancer globally, and catalyze the development of new studies and programmes"

2. Abstract: Page 2: Some, particularly, the major limitations of the study, as identified in the comments of the second reviewer, need to be stated in the abstract.

As per the BMJ Open research article submission guidelines (http://bmjopen.bmj.com/pages/authors/), limitations are to be stated in the "strengths and limitations" section of the manuscript that follows the abstract. Please note that in the "strengths and limitations" section of the manuscript, we have already stated: "Costs of the ASPIRE trial are retrospective as the trial was not designed to evaluate cost-effectiveness. Therefore, costs may reflect study as opposed to real world conditions." We have added a new bullet point in the "strengths and limitations" section that addresses the other reviewer's earlier comments about the limitations of our study.

p. 3 "We also did not consider human resource and capacity constraints in the Ugandan health system."

3. Page 7: lines 50-51: Replace "ASPIRE cost data was not available" with "ASPIRE cost data were not available".

The suggested change has been made.

p.7 "ASPIRE cost data was were not available"

4. Page 16: "These results should assist in program planning to implement approaches to reduce the burden of cervical cancer globally, and catalyze the development of new studies and programmes." Is respect of the statement above, I suggest the authors are more specific with their recommendations. For example, which type of study and of what focus does the result of this study engender; which of the strategies considered in this study require further study to understand it contribution to reducing the burden of cervical cancer globally.

Please refer to our response to comment 1 for the specific recommendation that we have added. In addition, please note the following recommendations that are already in the manuscript:

- p. 16 "It is of note that all the women in this study had access to a mobile phone. This may not be the case in rural and remote areas of Uganda, so novel screening approaches may need to be developed that would be more suitable for these locations."
- P. 16 "Moving forward, developing models that can evaluate the integrated delivery of primary care services will be critical to assess the wider impacts of new health care delivery methods in low resource settings, as well as to capture potential synergies associated with packaging interventions."

5. Figure 1: Do all the three cervical cancer prevention methods apply at all three points indicated by the broken arrows? I guess not, therefore, I suggest the authors present separate boxes for each of the methods of prevention; screening, diagnosis and treatment, showing where each applies in the scheme of the natural history for clarity.

We disagree with the reviewer's contention that screening, diagnosis and treatment do not each apply along the entire scheme of natural history. Please see the table below for an explanation:

We have added to the figure legend to enhance clarity.

In, addition, we have modified the box at the top of the figure to more explicitly state that screening, diagnosis and treatment apply to both pre-cancer and cancer.

Figure 1 legend: "Screening, diagnosis, and treatment of pre-cancer or cancer are determined by screening strategy."

Reviewer 2 (Joel Fokom Domgue):

1. In the revised version of the manuscript, the authors properly addressed the concerns raised by the reviewers.
We thank the reviewer for the positive feedback.

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